Parental Occupational Exposures to Electromagnetic Fields and Radiation and the Incidence of Neuroblastoma in Offspring

Anneclaire J. De Roos,[1] Kay Teschke,[2] David A. Savitz,[1] Charles Poole,[1] Seymour Grufferman,[3] Brad H. Pollock,[4] and Andrew F. Olshan[1]

We examined parental occupational exposures to electromagnetic fields and radiation and the incidence of neuroblastoma in offspring. Cases were 538 children diagnosed with neuroblastoma between 1992 and 1994 in the United States or Canada. Age-matched controls were selected by random-digit dialing. Occupational exposures to electrical equipment and radiation sources were classified by an industrial hygienist, and average exposures to extremely low frequency magnetic fields were estimated using a job exposure matrix. Maternal exposure to a broad grouping of sources that produce radiofrequency radiation was associated with an increased incidence of neuroblastoma (odds ratio = 2.8; 95% confidence interval = 0.9–8.7). Paternal exposure to battery-powered forklifts was positively associated with neuroblastoma (odds ratio = 1.6; 95% confidence interval = 0.8–3.2), as were some types of equipment that emit radiofrequency radiation (odds ratios ≅2.0); however, the broad groupings of sources that produce ELF fields, radiofrequency radiation, or ionizing radiation were not associated with neuroblastoma. Paternal average extremely low frequency magnetic field exposure >0.4 microTesla was weakly associated with neuroblastoma (odds ratio = 1.6; 95% confidence interval = 0.9–2.8), whereas maternal exposure was not. Overall, there was scant supportive evidence of strong associations between parental exposures in electromagnetic spectrum and neuroblastoma in offspring. (EPIDEMIOLOGY 2001; 12:508–517)

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Exposures within the electromagnetic spectrum are extremely diverse, covering an enormous range of frequencies. At the high end of the electromagnetic spectrum (10^{16}-10^{22} Hertz [Hz], or cycles per second), radiation is ionizing, meaning it can break molecular bonds. At the opposite end of the spectrum (3–3,000 Hz), extremely low frequency (ELF) electric and magnetic fields are non-ionizing, but are of particular concern because of ubiquitous exposure from myriad sources, including electric power lines, computers, and household appliances, which are powered by 60-Hz frequency currents in North America. Radiofrequency radiation, like ELF fields, is non-ionizing, but is produced by much higher frequencies (10^5–10^9 Hz) from a variety of sources such as radio and television broadcasting, cellular telephones, radionavigation, amateur radio, and mobile radio. These frequencies differ in how they interact with biological tissues; at frequencies above 10^5 Hz, tissues absorb energy radiated from electromagnetic fields, while at lower frequencies tissues couple with the electric field and the magnetic field separately, inducing electric currents.[1]

There has been ongoing interest in the possibility that parental exposures to electromagnetic fields and radiation may cause cancers in offspring, either through a mechanism involving direct exposure to the developing fetus *in utero*, or through a germline mutation in the father or mother before conception. Clearly, ionizing radiation is a human carcinogen and a demonstrated reproductive hazard in animals,[2,3] but the potential for transgenerational carcinogenesis in humans is unclear. The evidence for adverse reproductive outcomes from exposures to lower frequencies of the electromagnetic spectrum is even less clear. The overall evidence on genotoxicity of ELF fields is not convincing, although some specific exposure scenarios may have greater po-

From [1]Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC; [2]Department of Health Care Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada; [3]Department of Family Medicine and Clinical Epidemiology, School of Medicine, University of Pittsburgh, Pittsburgh, PA; and [4]University of Florida, Pediatric Oncology Group Statistical Office and the Department of Health Policy and Epidemiology, Gainesville, FL.

Address correspondence to: Anneclaire J. De Roos, Children's Cancer Group, P.O. Box 60012, Arcadia, CA 91066-6012; e-mail: deroosa@mail.nih.gov

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tential to cause genotoxic effects, such as ELF fields in combination with a chemical mutagen or ionizing radiation.[4,5] Similarly, there are no consistent data supporting biologic effects of radiofrequency radiation.[6,7]

Several studies have examined associations between parental occupation and the incidence of neuroblastoma in offspring.[8–12] Paternal occupations with likely exposure to elevated ELF fields (electricians, electric and electronics workers, linemen, utility employees, welders, electric equipment repairmen) were positively associated with neuroblastoma in some study populations,[9,10] although no clear association was observed for such jobs in other studies.[8,11] In our previous analysis of parental job title within the same study population as the current analysis,[12] an increased rate of neuroblastoma was estimated for fathers or mothers working as electrical power installers or power plant operators, and fathers working as broadcast, telephone, and dispatch operators; however, employment as electricians, welders, or in electrical equipment assembly or repair were not positively associated. In a recent cohort study in which ELF magnetic field levels were estimated using a job exposure matrix, no consistent pattern of effect was observed for maternal or paternal exposures and the risk of neuroblastoma in offspring.[13]

Although the results from some of these studies are suggestive, exposures were inferred from occupation or job title rather than from descriptions of work activities or use of electrical equipment. To evaluate more specifically the effects of parental occupational exposures to electric and magnetic fields and radiation on the incidence of neuroblastoma in offspring, we analyzed data from our large, multicenter case-control study, using detailed exposure information to estimate the effects associated with different sources and frequencies.

Methods

Study Population

The study population for this case-control study of neuroblastoma is described in detail elsewhere.[12] In brief, cases were patients under the age of 19 years with a confirmed new diagnosis of neuroblastoma between May 1, 1992, and April 30, 1994, registered at any of 139 participating hospitals in the United States and English-speaking Canada. The hospitals were members of either of two pediatric collaborative clinical trials groups, the Children's Cancer Group or the Pediatric Oncology Group. The treating physicians provided consent to approach the parents for participation. Of the families contacted, we enrolled 538 cases (73% of those eligible). The 538 enrolled neuroblastoma cases had ages at diagnosis ranging from newborn to 17 years, with a mean of 2.2 years, and 56% of cases were male.

One control for each of 504 cases was selected by random-digit dialing (RDD). We were unable to recruit controls successfully for the remaining 34 cases after multiple attempts. Controls were individually matched to cases on date of birth ($\pm$6 months for cases $\leq$3 years of age, $\pm$1 year for cases $>$3 years of age). The response proportion for the RDD screening was 74%, calculated as the percentage of households who participated of the total number selected for screening,[14] and recruitment among those eligible was 71%.

Data Collection

A telephone interview was conducted with each mother and with the father when available. We obtained interviews from all mothers (538 case mothers and 504 control mothers), 472 case fathers (88% of enrolled cases; 405 direct and 67 proxy interviews with the mother), and 445 control fathers (89% of enrolled controls; 304 direct and 141 proxy interviews with the mother). The interview included questions on demographic characteristics such as parental age, race, education, and income. An occupational history was obtained from each parent, including dates of employment, names of employers, occupations, industries, job titles, specific duties, and hours per week. For each job held during the 2-year period before the child's date of birth, mothers and fathers were asked if they worked within 30 feet of any electrical equipment or radiation sources ("sources"). Respondents could report exposure to any of 47 sources listed in an interview guide, as well as to any other source. For each source reported, data were collected on the average distance from the source, hours per week spent working near the source while it was turned on, and the dates exposure began and ended.

Because proxy respondents for the fathers' interviews were not asked questions from the occupational section on exposures to electrical equipment or radiation sources, approximately 200 fathers were not included in the analyses of paternal occupational exposures. In addition, two mothers and three fathers refused to answer the questions regarding these exposures. Data on electrical equipment and radiation sources were available for a total of 1,040 mothers (537 case mothers, 503 control mothers) and 707 fathers (405 case fathers, 302 control fathers).

Exposure Assessment

Self-reported information on occupation was combined with self-reported exposures to sources to perform several levels of exposure assessment.

Self-Reported Exposure to Sources

A parent was coded as exposed to a specific source if he or she reported exposure to that source in any job.

Industrial Hygienist's Review of Self-Reported Exposure to Sources

Each report of exposure to a specific source was reviewed by an industrial hygienist (IH), blinded to case or control parent status and the parent's gender. The review was intended to increase specificity of exposure measures by reclassifying those with unlikely exposures to sources. All reported information for each exposure was reviewed, including industry, occupation, employer's product, job title, job duties, hours of exposure per week while the source was turned on, average distance from the source, the dates exposure began and ended, and the

TABLE 1. Electric Equipment and Radiation Sources, Grouped by Major Electromagnetic Frequency

Extremely low frequency electric and magnetic fields
Electrolytic cell
Brazing furnace
Solder pot or bath
Soldering iron (1 ft.)*
Arc welding machine, DC†
Arc welding machine, AC†
Arc welding machine, AC-high frequency
Plasma arc welding and cutting machine
Large electric motors (15 ft.)
Battery-powered forklift or other mobile equipment (1 ft.)
Induction heater or furnace
Hydroelectric power generation plant
Thermoelectric power generation plant
Nuclear power generation plant
Electric power transmission lines, live (30 ft.)
Electric power distribution lines, live
Electric power distribution substation
Radiofrequency radiation
Shortwave diathermy unit
Radiofrequency heater, sealer, or edge glue dryer; shielded
Radiofrequency heater, sealer, or edge glue dryer; unshielded (30 ft.)
Cellular phone (1 ft.)
Mobile radio transmitter, less than 7 Watts power (1 ft.)
Mobile radio transmitter, greater than 7 Watts power
Television broadcasting transmission tower or antenna
FM radio antenna
AM radio broadcast tower (30 ft.)
Radar, rotating (15 ft.)
Radar, stationary (30 ft.)
Microwave transmission
Ionizing radiation
X-ray machine
Nuclear power generation plant
Non-destructive testing radiation sources (30 ft.)
Radioisotopes
Nuclear gauges or radioactive gauges
Other ionizing radiation sources

* Maximum critical distance in parentheses where different from 3 feet.
† DC = direct current; AC = alternating current.

use of protective equipment or clothing. Based on this exposure information, a parent was classified as unexposed (in all jobs), possibly exposed (in any job), or probably exposed (in any job) to the source. Each exposure scenario was evaluated on an individual basis, and professional but subjective judgment was used; in addition, there were two objective criteria for reclassifying parents as unexposed. Parents who reported working near the source for an average of zero hours per week while the source was turned on were reclassified as unexposed. Parents who reported working at an average distance greater than a prespecified maximum critical distance were reclassified as unexposed. The maximum critical distance values were developed in consultation with a professional health physicist, and were intended to distinguish groups of persons in situations with high exposure. The maximum critical distance for most sources was 3 feet, with some exceptions noted in Table 1.

Grouping of Sources by Major Frequency

Although many sources can simultaneously emit electromagnetic energy of different frequencies (eg, equipment that uses a 60-Hz power source to convert to energy of another frequency such as x-ray machines, radiofrequency sealers, some types of welding equipment), some sources produce notably high levels of a specific frequency. Sources were grouped by the major frequency produced, so that dichotomous exposure variables representing self-reported, possible, and probable high exposure to extremely low frequency electric and magnetic fields (ELF EMF), radiofrequency radiation, and ionizing radiation were created (see Table 1).[6,15]

Assignment of Extremely Low Frequency Magnetic Field Values from Job Exposure Matrix

We compiled published occupational extremely low frequency magnetic field (ELF MF) values into a job exposure matrix (JEM) (available upon request). The JEM only included studies in which time-weighted-average 60-Hz magnetic field values based on personal measurements were reported as the arithmetic mean, or in a metric that could be converted to the arithmetic mean.[15–35] The length of measurement in the different studies ranged between 1 hour to 1 full week. No area or spot measurements were included in the JEM. ELF MF exposure levels measured in specific jobs were assigned from the JEM to jobs in our study, which allowed estimation of an average occupational ELF MF exposure in microTesla (μT) for each parent. Each job held within the 2-year period before the birth of the index child was reviewed, and all appropriate values from the JEM were included in calculation of an average ELF MF exposure for that job, weighted by the number of measurements taken for each published value. Where a person had probable exposure (based on IH-review of self-report) to electrical equipment or radiation sources in a job, we averaged the published ELF MF values for the person's job with values for jobs in which exposure to the type of equipment is normally prevalent, weighted by the hours per week spent in the job and in exposure to the equipment. For example, if a mechanic who worked 40 hours per week in his job reported using welding equipment for 5 hours per week, then we calculated the person's average ELF MF exposure for that job by averaging values from the JEM for mechanic, non-welding (weighted by 40) with values from the JEM for welders (weighted by 5). Where a person held more than one job during the 2-year time period, the average ELF MF exposures were averaged over all jobs, weighted by the person's duration at each job. Parents who did not work during the time period of interest were assigned a background ELF MF level based on residential and non-work hour measurements published in the literature.[15,21,22,34,36,37]

Two raters (one industrial hygienist and one epidemiologist) conducted the assignment of ELF MF values from the JEM to jobs in our study, and their two calculated average exposures for each job were averaged to obtain a final average occupational ELF MF exposure for each job. Agreement between the two raters was good, with agreement between categories of assigned exposure ($\leq$0.12, >0.12–0.2, >0.2–0.3, >0.3–0.4, >0.4–0.5, and >0.5 μT), as estimated by the Kappa statistic, of κ = 0.74 (95% confidence interval [CI] = 0.71–0.76).

TABLE 2. Estimated Effects of Maternal Occupational Exposures to Electric Equipment and Radiation Sources on the Incidence of Neuroblastoma in Offspring*

	Self-Reported Exposure				IH-Reviewed Exposure Possible				IH-Reviewed Exposure Probable			
	Exposed				Exposed				Exposed			
	Case	Control	OR†	95% CI	Case	Control	OR†	95% CI	Case	Control	OR†	95% CI
Equipment												
Cellular phone	8	4	1.8	0.5–6.0	5	2	1.1	0.5–2.3	5	2	2.1	0.4–11.0
Large electric motor	2	9	0.2	0.1–1.0	2	7	0.8	0.5–1.3	0	0		
X-ray machine	22	23	1.0	0.6–1.9	4	2	1.6	0.8–3.2	4	2	2.1	0.4–11.4
Equipment grouped by major frequency												
Power-frequency fields (ELF EMF‡)	16	23	0.7	0.3–1.3	10	14	0.8	0.5–1.2	4	4	0.9	0.2–3.7
Radiofrequency radiation	16	12	1.2	0.6–2.6	13	4	1.2	0.8–2.0	12	4	2.8	0.9–8.7
Ionizing radiation	25	24	1.1	0.6–2.0	4	3	1.2	0.3–4.5	4	3	1.4	0.3–6.4

* n = 537 case mothers, 503 control mothers.
† Adjusted for child's age, maternal race, maternal age, and maternal education.
‡ ELF EMF = extremely low frequency electric and magnetic fields; OR = odds ratios.

CODING OF COVARIATES

Demographic characteristics of interest included maternal education, maternal race, and maternal age at birth of the index child. The characteristics were coded using an indicator variable for each of the following categories: maternal education (less than high school graduate, high school graduate and/or some college, college degree or more as the referent), maternal race (white as the referent, black, Hispanic, other), and maternal age at birth of the index child ($<$18 years, 18–39 years as the referent, $\geq$40 years).

Although it is not known whether parental occupational chemical exposures can cause neuroblastoma, these exposures are highly associated with occupational electromagnetic fields and radiation and could thus potentially confound the effects estimated in this study. Parental occupational chemical exposures were evaluated as potential confounders, using indicator variables representing broad categories of exposure to halogenated hydrocarbons, nonvolatile hydrocarbons, volatile hydrocarbons, metals, and paints.

STATISTICAL ANALYSES

Separate analyses were conducted for maternal and paternal exposures. The number of parents exposed to each source was tabulated. Where the frequency of IH-reviewed possible exposure was five or greater, exposure odds ratios were calculated using unconditional logistic regression to estimate the rate ratios for neuroblastoma associated with self-reported exposure, IH-reviewed possible exposure, and IH-reviewed probable exposure. Exposure to each source was evaluated in a separate model, using those unexposed to that source as the reference group. Each model included variables for the matching factor, child's age, coded as a set of indicator variables (6-month intervals for ages $\leq$3 years; 2-year intervals for ages $>$3–11 years, one variable for ages $>$11 years). Each model also included indicator variables for the demographic covariates. Potential confounding by occupational chemical exposures was considered by simultaneously adjusting for the broad chemical categories.

Associations between parental average occupational ELF MF exposure and neuroblastoma incidence were examined by modeling ELF MF exposure as a set of indicator variables for each parent, representing increasing levels of exposure. Exposure categories were chosen in an effort to best represent trends in the data while keeping precision high, based on examination of quadratic spline curves using different knots[38] and regression analyses using different cutpoints (results not shown). The reference category was chosen to represent a "background" exposure, and the cutpoint was selected based on the exposure distribution for each parent. Maternal exposure variables represented $>$0.12–0.2 μT, $>$0.2–0.3 μT, and $>$0.3 μT, leaving exposures $\leq$0.12 μT as the reference category. Paternal exposure variables represented $>$0.15–0.2 μT, $>$0.2–0.3 μT, $>$0.3–0.4 μT, and $>$0.4 μT, leaving exposures $\leq$0.15 μT as the reference category. The ELF MF indicator variables for each parent's exposure were included in an unconditional logistic regression model, along with variables for child's age and the set of demographic covariates. We addressed potential confounding of the estimated effects by occupational chemical exposures by simultaneously adjusting for the broad chemical categories. We evaluated effect measure modification for combined paternal occupational exposures to high average ELF MF ($>$0.4 μT) and chemical categories by estimating the effects of joint and individual exposures. Maternal chemical exposures were too infrequent to allow examination of interactions with ELF MF exposure.

Results

The frequencies and effect estimates for maternal and paternal occupational exposures to electrical equipment and radiation sources are shown in Tables 2 and 3, respectively. There are substantial differences in the numbers of exposed subjects based on self-report or IH-

TABLE 3. Estimated Effects of Paternal Occupational Exposures to Electric Equipment and Radiation Sources on the Incidence of Neuroblastoma in Offspring*

	Self-Reported Exposure				IH-Reviewed Exposure Possible				IH-Reviewed Exposure Probable			
	Exposed				Exposed				Exposed			
	Case	Control	OR†	95% CI	Case	Control	OR†	95% CI	Case	Control	OR†	95% CI
Equipment												
Battery-powered forklift or other mobile equipment	38	27	1.0	0.6–1.7	25	12	1.6	0.8–3.2	25	12	1.6	0.8–3.2
Cellular phone	34	23	1.2	0.7–2.1	17	13	1.1	0.5–2.3	17	13	1.1	0.5–2.3
Electric power distribution lines	10	11	0.6	0.2–1.4	3	2	1.1	0.2–6.8	0	0		
Electric power transmission lines, live	7	9	0.5	0.2–1.4	7	9	0.5	0.2–1.4	5	3	1.2	0.3–5.1
Electrolytic cell	8	4	1.5	0.4–5.2	5	3	1.2	0.3–5.0	0	0		
FM radio antenna	13	9	0.9	0.4–2.4	7	4	1.2	0.3–4.3	3	1	1.7	0.2–17.1
Induction heater or furnace	7	5	1.0	0.3–3.1	7	4	1.2	0.3–4.2	1	1	0.7	0.1–11.5
Large electric motor	45	42	0.7	0.5–1.2	34	30	0.8	0.5–1.3	0	0		
Laser	8	10	0.7	0.3–1.7	2	6	0.3	0.1–1.3	2	6	0.3	0.1–1.3
Mobile radio transmitter, >7 Watts power	14	11	0.9	0.4–2.1	10	8	0.9	0.3–2.4	10	8	0.9	0.3–2.4
Mobile radio transmitter, <7 Watts power	26	13	1.5	0.7–3.0	20	7	2.1	0.9–5.2	20	7	2.1	0.9–5.2
Radar- stationary	9	4	1.6	0.5–5.4	9	4	1.6	0.5–5.4	9	3	2.2	0.6–8.3
Soldering iron	35	21	1.2	0.7–2.2	15	12	0.9	0.4–1.9	15	12	0.9	0.4–1.9
Solder pot or bath	8	3	2.0	0.5–7.7	3	2	1.2	0.2–7.1	0	0		
Welding machine, arc AC‡	32	20	1.2	0.7–2.2	14	8	1.2	0.5–3.0	14	8	1.3	0.6–2.9
Welding machine, arc AC-high frequency	11	7	1.2	0.5–3.2	6	1	4.7	0.6–39.9	6	1	4.7	0.6–39.9
Welding machine, arc DC‡	32	24	1.0	0.6–1.7	18	10	1.3	0.6–3.0	18	10	1.3	0.6–3.0
Welding machine, plasma arc	6	6	0.7	0.2–2.2	4	3	0.9	0.2–4.3	4	3	0.9	0.2–4.3
Welding machine, any type§	52	33	1.5	1.0–2.4	25	14	1.6	0.8–3.2	25	14	1.6	0.8–3.2
Equipment grouped by major frequency												
Power-frequency fields (ELF EMF‡)	113	90	0.8	0.6–1.2	73	60	0.8	0.5–1.2	57	34	1.2	0.8–1.9
Radiofrequency radiation	72	48	1.2	0.8–1.8	50	32	1.2	0.8–2.0	45	27	1.3	0.8–2.2
Ionizing radiation	17	10	1.5	0.7–3.3	5	4	1.2	0.3–4.5	5	4	1.2	0.3–4.5

* n = 405 case fathers, 302 control fathers.
† Adjusted for child's age, maternal race, maternal age, and maternal education.
‡ ELF EMF = extremely low frequency electric and magnetic fields; AC = alternating current; DC = direct current; OR = odds ratios.
§ Includes AC, AC-high frequency, argon, DC, MIG, plasma, spot, wire, and not otherwise specified welding equipment.

review. Over 94% of reports that were recoded as unexposed, and 70% of reports that were recoded as possibly exposed, were done so based on the prespecified objective criteria concerning hours per week and distance from the source. Our observation in the IH exposure review was that these somewhat arbitrary objective criteria were effective at separating highly exposed persons from persons exposed at lower levels, in many cases clearly distinguishing persons who were actually using a type of equipment from others who were simply working nearby. Sources with IH-reviewed possible exposure frequencies of less than 5 were not further analyzed and are therefore not listed in Tables 2 and 3, although these sources are counted in the groupings of sources by the major electromagnetic frequency produced.

Maternal exposure to electrical equipment and radiation sources was infrequent, thus very few sources were analyzed (see Table 2). Maternal use of cellular telephones (odds ratio [OR] = 2.1; 95% CI = 0.4–11.0) and x-ray machines (OR = 2.1; 95% CI = 0.4–11.4) were each associated with an approximate twofold increased incidence of neuroblastoma in offspring, although these estimates were very imprecise. The broad grouping of exposure to radiofrequency radiation was associated with a nearly threefold increased incidence of neuroblastoma (OR = 2.8; 95% CI = 0.9–8.7). The summary measure of exposure to ELF fields was not associated with neuroblastoma.

There was some evidence for associations between paternal exposures to electrical equipment and radiation sources and neuroblastoma in offspring (see Table 3). A few sources that produce strong ELF fields were positively associated with neuroblastoma. For example, operating battery-powered forklifts or other mobile equipment was associated with a 60% increased incidence of neuroblastoma (OR = 1.6; 95% CI = 0.8–3.2). Probable exposure to any type of welding equipment (including AC, AC-high frequency, argon, DC, metal inactive gas (MIG), plasma, spot, wire, and not otherwise specified welding) was associated with a 60% increased incidence of neuroblastoma, and use of AC-high frequency arc welding machines had a nearly fivefold increased, but imprecise, effect estimate. When adjusting for occupational exposures to chemicals (results not shown), paternal exposure to any type of welding equipment was no longer associated with neuroblastoma; however, the odds ratio for AC-high frequency welding equipment remained elevated, albeit very imprecise (OR = 3.6; 95% CI = 0.4–32.4). None of the other sources of ELF fields was positively associated with neuroblastoma. There was some indication that paternal exposures to sources of radiofrequency radiation were positively asso-

TABLE 4. Estimated Effects of Parental Average Occupational Extremely Low Frequency Magnetic Field Exposure (in micro Tesla, μT) on the Incidence of Neuroblastoma in Offspring*

	Paternal Exposure					Maternal Exposure				
		Exposed					Exposed			
	Exposure	Case	Control	OR†	95% CI	Exposure	Case	Control	OR†	95% CI
Indicator variables representing increasing exposure levels	≤0.15 μT	67	47	1.0		≤0.12 μT	166	142	1.0	
	>0.15–0.2 μT	132	104	0.9	0.6–1.5	>0.12–0.2 μT	239	249	0.9	0.7–1.2
	>0.2–0.3 μT	119	89	0.9	0.6–1.5	>0.2–0.3 μT	99	73	1.3	0.9–1.9
	>0.3–0.4 μT	47	43	0.8	0.4–1.3	>0.3 μT	33	39	0.8	0.5–1.3
	>0.4 μT	40	19	1.4	0.7–2.8					
High versus low exposure	≤0.4 μT	365	283	1.0		≤0.3 μT	505	466	1.0	
	>0.4 μT	40	19	1.6	0.9–2.8	>0.3 μT	33	39	0.8	0.5–1.3
Adjusted for chemical exposures‡	≤0.4 μT	365	283	1.0		≤0.3 μT	505	466	1.0	
	>0.4 μT	40	19	1.3	0.7–2.4	>0.3 μT	33	39	0.8	0.5–1.3

* n = 405 case fathers, 302 control fathers; n = 537 case mothers, 503 control mothers.
† Adjusted for child's age, maternal race, maternal age, and maternal education.
‡ Chemical categories: volatile hydrocarbons, nonvolatile hydrocarbons, halogenated hydrocarbons, metals, and paints.

ciated with neuroblastoma. Exposure to mobile radio transmitters, <7 Watts power (OR = 2.1; 95% CI = 0.9–5.2) and stationary radar sources (OR = 2.2; 95% = 0.6–8.3) were each associated with an approximate two-fold increased incidence of neuroblastoma; these associations remained elevated after adjusting for occupational exposures to chemicals. The variables representing sources grouped by the major electromagnetic frequency indicated that ELF EMF, radiofrequency radiation, and ionizing radiation were only very weakly associated with neuroblastoma. After adjusting for occupational exposures to chemicals, the odds ratio for paternal ELF EMF exposure was diminished to the null value (OR = 1.0; 95% CI = 0.6–1.7).

Results from analyses of maternal and paternal average occupational ELF MF exposure categorized as a series of indicator variables representing increasing levels of exposure are shown in Table 4. Although the effect estimate for maternal ELF MF exposure between 0.2 and 0.3 μT is slightly elevated (OR = 1.3; 95% CI = 0.9–1.9), there is no consistent pattern of effect. The effect estimates for paternal ELF MF exposures are close to the null value, except for exposures higher than 0.4 μT, suggesting that any effects occur past an upper threshold of exposure. Children whose fathers' average occupational ELF MF exposures were higher than 0.4 μT were 60% more likely to have neuroblastoma than children of fathers with lower exposures (OR = 1.6; 95% CI = 0.9–2.8). This association was diminished when adjusting for paternal exposures to chemicals, although a weak association remained (OR = 1.3; 95% CI = 0.7–2.4).

The estimated joint and individual effects of paternal occupational ELF MF and chemical exposure combinations are presented in Table 5. There is no indication of superadditivity of the effects of high ELF MF (>0.4 μT) and chemical exposure combinations on the incidence of neuroblastoma; although the effect estimate for joint exposure to ELF MF and halogenated hydrocarbons suggests supperadditivity, the small number of persons with joint exposure limits interpretation.

Discussion

In this study, which employed extensive assessment of parental occupational exposures to electrical equipment and radiation sources, there was evidence against strong associations between ELF EMF and increased incidence of neuroblastoma in offspring. Although paternal exposures to a few types of electrical equipment were associated with neuroblastoma, most others were not, and some of the observed associations were diminished after

TABLE 5. Estimated Individual and Joint Effects of Paternal Occupational Exposures to Average Extremely Low Frequency Magnetic Field Strengths >0.4 μT and Chemicals on the Incidence of Neuroblastoma in Offspring*

Occupational Exposures	Number Exposed	Odds Ratio†	95% CI
ELF MF‡ and halogenated hydrocarbons			
Joint exposure	8	5.1	0.6–41.8
ELF MF only	51	1.3	0.7–2.4
Halogenated hydrocarbons only	52	0.7	0.4–1.3
Neither	596	1.0	
ELF MF and nonvolatile hydrocarbons			
Joint exposure	30	2.2	0.9–5.0
ELF MF only	29	1.3	0.6–2.8
Nonvolatile hydrocarbons only	109	1.3	0.9–2.1
Neither	539	1.0	
ELF MF and volatile hydrocarbons			
Joint exposure	33	1.9	0.9–4.2
ELF MF only	26	1.5	0.7–3.5
Volatile hydrocarbons only	156	1.4	1.0–2.1
Neither	492	1.0	
ELF MF and paints			
Joint exposure	12	1.4	0.4–5.0
ELF MF only	47	1.6	0.8–3.0
Paints only	50	0.9	0.5–1.6
Neither	598	1.0	
ELF MF and metals			
Joint exposure	16	2.3	0.7–7.2
ELF MF only	43	1.4	0.7–2.7
Metals only	45	1.1	0.6–2.1
Neither	603	1.0	

* n = 405 case fathers, 302 control fathers.
† Adjusted for child's age, maternal race, maternal age, and maternal education.
‡ ELF MF = extremely low frequency magnetic fields.

adjusting for exposure to chemicals in the workplace. There was some evidence that high average paternal occupational exposure to ELF MF (>0.4 μT), as assigned from a JEM, was weakly associated with neuroblastoma. Some positive associations were observed for maternal exposure to x-ray machines, and maternal and paternal exposures to sources of radiofrequency radiation, yet the low prevalences of such exposures in our study population precluded precise effect estimation.

Ours is the first study to examine associations between parental exposures in the electromagnetic spectrum and neuroblastoma in offspring using detailed self-reported exposures to electrical equipment and radiation sources. Such an improvement in detail of exposure information, however, introduces the possibility for recall bias. We have attempted to reduce potential bias of effect estimates resulting from differential recall between cases and controls by reviewing each reported exposure scenario carefully, blinded to disease status, so that situations in which exposure was unlikely were recoded as possibly exposed or unexposed. Surprisingly, exposure reports by case parents were less likely to be recoded as unexposed than those by control parents (results not shown), indicating that recall bias may not have affected reporting of exposures to electrical equipment and radiation sources. It is still possible that case parents were biased toward reporting shorter average working distances from equipment, or higher number of exposed hours per week, thus affecting our assessment. Case reports were more likely to be recoded for objective reasons (based on distance and hours per week criteria) than control reports, indicating some potential recall bias in this regard.

Although our previous examination of parental job title suggested positive associations between jobs with characteristically high ELF EMF exposure and the incidence of neuroblastoma in offspring,[12] this more detailed examination of specific sources indicated that, at best, the association is weak and inconsistent across different sources of ELF fields. Because the overall evidence for genotoxicity of these exposures is unconvincing,[4] there is little support for biologic mechanisms acting directly through germline mutations caused by maternal or paternal exposures. There are specific exposure scenarios that may have greater potential to cause genotoxic effects, such as intermittent exposure to ELF fields,[39] ELF fields in combination with high frequency transient exposures,[40] or ELF fields in combination with exposure to a chemical mutagen or other ionizing radiation.[4,5,41] There has been little epidemiologic research on potential biological effects of these more complex exposures, but in our study there was no indication of superadditive effects of exposure to ELF MF in combination with chemical exposures. Because the existing evidence for genotoxicity of ELF EMF is overwhelmingly negative, the carcinogenic potential of these exposures is thought to occur in some later stage of tumor development, which could point to the relevance of in-utero exposures. Studies in women, however, have had largely inconsistent results for outcomes such as childhood cancers, fetal loss, and congenital malformations.[42–44] In short, although there are *in vitro* data indicating that biochemical pathways such as gene transcription, ion transport across the cell membrane, cell growth, and melatonin synthesis may be affected by ELF fields,[4] a carcinogenic mechanism has yet to be identified, and our study did not contribute strong supportive evidence for transgenerational or *in utero* carcinogenesis of ELF fields.

Paternal welding has been the focus of many reproductive health studies because welding occupations are among those with the highest ELF EMF exposures. Several studies have found positive associations with paternal welding and other types of childhood cancers.[45–47] Although our previous job title analysis did not reveal any positive association of paternal welding occupations with neuroblastoma (OR = 0.5; 95% CI = 0.1–1.6), only 13 fathers held these jobs.[12] In this analysis of specific types of welding equipment, there were 39 fathers with probable exposures to welding equipment. Exposure to any type of welding machine was positively associated with neuroblastoma, but this association was diminished after adjusting for occupational chemical exposures. We did, however, observe a positive but very imprecise association with AC-high frequency arc welding. Welding operations can produce exposures to frequencies in the ultraviolet, visible, infrared, and radiofrequency ranges, in addition to the ELF range,[15,48] and AC-high frequency welding specifically emits high frequency fields in the kHz range in addition to the current frequency of 60 Hz.[49] There is little information on the potential biologic effects of simultaneous exposures to multiple frequencies in the electromagnetic spectrum, such as those incurred in high frequency welding.

Our data suggested an increased incidence of neuroblastoma associated with maternal and paternal exposures to certain sources of radiofrequency radiation, and maternal exposure to radiofrequency radiation in the aggregate. It is interesting to note that our previous analysis of paternal employment found an estimated sixfold increased rate of neuroblastoma in offspring of fathers working as broadcast, telephone, or dispatch operators.[12] Although radiofrequency radiation, like ELF fields, is non-ionizing, it is a completely different entity with different physical properties. With the ability to vibrate molecules and heat tissues, biologic effects of radiofrequency radiation related to temperature increases have been consistently reported, but non-thermal effects have not been substantiated.[6] There is little evidence for genotoxic, embryopathic, or teratogenic effects at or below the maximum permissible exposures, and no consistent effects at levels much higher than the maximum permissible exposures.[6,7] Most animal studies, however, have used only a few frequencies in the radiofrequency spectrum, and most of the studies have used acute high exposures rather than low-level chronic exposures. Although our results are suggestive, a viable biologic mechanism has yet to be identified for a causal relation between parental exposures to radiofrequency radiation and neuroblastoma in offspring.

In our study, maternal exposure to x-ray machines was associated with a twofold increased incidence of neuroblastoma in offspring; however, with only 6 exposed mothers, this estimate was imprecise. Although occupational exposures of medical workers to ionizing radiation have declined considerably since the International Commission on Radiological Protection revised its recommendations on maximum permissible dose in 1977,[50] medical workers do receive small doses of radiation, at an average of 0.7 millisieverts per year.[51] It is well known that ionizing radiation is mutagenic and carcinogenic to adults, and there are some fairly convincing data that in-utero medical radiation exposures are associated with an increased risk of childhood cancer.[2,52] The association between x-ray machines and neuroblastoma observed in our study is interesting and has biological plausibility, but the low prevalence of exposure limits interpretation.

A comprehensive review of the published literature allowed assignment of average occupational ELF MF exposure values to jobs held by parents in our study. This method of assigning values for ELF MF from the literature to estimate exposures has recently been employed in other case-control and cohort studies.[13,53–56] Estimation of average occupational ELF MF exposure allowed examination of the predicted odds of neuroblastoma along a continuum of exposure. We did not see any strong association between average occupational ELF MF exposure and neuroblastoma incidence in offspring, but we observed a weak positive association for paternal exposure $>0.4\ \mu T$. These results may reflect truly weak or null associations; conversely, it is possible that stronger or more consistent associations were obscured by limitations of the exposure assessment method. Most notably, ELF MF exposure estimated in this manner only approximates average exposure of persons within a certain occupation, and exposure studies indicate that the variability between workers within an occupation is high.[57] Nevertheless, such a method of assigning exposures offers a feasible alternative when collecting actual exposure measurements is not economically or temporally possible. Another limitation of our ELF MF exposure estimation is that the assigned values represent only occupational exposure. ELF magnetic fields in a typical United States home vary widely, ranging from 0.05 to $0.4\ \mu T$,[15] and it is possible that we did not see an association because our measure of ELF MF only in occupation was not representative of the exposure ranking that would occur if 24-hour ELF MF exposure values were available. Unfortunately, we did not have sufficient information on residence to assign non-work ELF MF values in the same manner as we did occupational ELF MF values. Finally, our ELF MF exposure estimation method is limited by its dependence on published occupational ELF MF measurements. Some jobs had many published values (*eg*, electric utility workers, welders, secretaries, managers, retail workers, teachers), while others had few or none (*eg*, hairdressers and cosmetologists, photographers, assemblers, inspectors, packagers and wrappers). Because published ELF MF values for general occupational groups (eg, artists, factory workers, general laborers) were assigned to jobs for which more specific descriptors were not available, parents in these professions are more likely to have been misclassified. Application of this method of exposure assessment should improve as data on ELF MF exposures in more types of jobs become available.

Lack of strong or consistent associations may have falsely resulted from our choice to assign average ELF MF values as the representative exposure metric. Average ELF MF strength may be less relevant in its association with neuroblastoma than another aspect of parental ELF MF exposure such as amount of time spent above or below certain threshold values; minimum, maximum, or geometric mean exposures; transient exposures (short bursts of exposure when equipment is turned on or off); or the intermittency of exposures. Other aspects of ELF fields could also be relevant, such as ELF electric fields, ELF fields in combination with high-frequency transient exposures, or the entire frequency content of the electromagnetic exposure. We chose the average ELF MF exposure because of its wide availability across published studies, as well as its high correlation with other exposure metrics (90th percentile, geometric mean, median, low and high cutoff scores, peak values, and time above a threshold).[58,59] Some aspects of exposure, however, such as lower ELF MF threshold measures,[58,59] rapid changes in the field, and high-frequency transients[59] are not likely to be highly correlated with the average ELF MF exposure; therefore, these types of exposures may not be fairly represented by our exposure assessment method.

Despite the limitations, the data presented here are the most extensive to date in describing associations between parental occupational exposures to electromagnetic fields and radiation and neuroblastoma in offspring. These data provide evidence against strong associations between parental ELF EMF exposures and neuroblastoma. The data indicate that any effect of paternal exposure to ELF MF is probably weak, and likely occurs only past an upper threshold of exposure. Our results indicate possible effects of maternal and paternal radiofrequency exposures on neuroblastoma, but, the sparse data do not allow firm conclusions. Some observed associations between sources of electromagnetic energy and neuroblastoma were completely diminished after adjusting for occupational chemical exposures, indicating the importance of detailed occupational exposure information in order to estimate specific effects.

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ERRATA

We regret the following compositor errors were made in the July 2001 issue of EPIDEMIOLOGY.

Watkins ML, Botto LD. Maternal prepregnancy weight and congenital heart defects in the offspring (pp. 439–446). The volume number in the abstract and the running head should be 12.

Grosso LM, Rosenberg KD, Belanger K, Saftlas AF, Leaderer B, Bracken MB. Maternal caffeine intake and intrauterine growth retardation (pp. 447–455). The volume number in the abstract and the running head should be 12. The month in the running head should be July.